Allergology International. 2011;60:483-489
DOI: 10.2332/allergolint.10-OA-0285

ORIGINAL ARTICLE

Delay of Onset of Symptoms of Japanese Cedar Pollinosis by Treatment with a Leukotriene Receptor Antagonist

Minoru Gotoh[1], Hidenori Suzuki[2] and Kimihiro Okubo[1]

ABSTRACT

Background: Leukotriene receptor antagonists (LTRAs) are effective for prophylactic treatment of pollinosis based on studies showing that administration of LTRAs prior to or at the start of the pollen season reduces symptoms and QOL disturbance at the peak of pollen dispersal. Two goals of prophylactic treatment of pollinosis are use of fewer types of drugs and delay of onset of symptoms and impairement of QOL. Therefore, this study was performed to determine if pranlukast, a LTRA, met these goals in treatment of pollinosis.

Methods: Pranlukast or placebo was administered to patients who visited our hospital immediately before the start of Japanese cedar pollen dispersal. The study was performed for 4 weeks as a double blind randomized trial. Subsequently, all patients were given pranlukast for a further 4 weeks from the peak until the end of pollen dispersal. The incidence of symptoms and use of concomitant drugs were investigated from daily nasal allergy records kept by patients. QOL was evaluated using the JRQLQ questionnaire.

Results: In the double blind period of the study, the percentage of patients who used concomitant drugs for nasal symptoms was significantly lower in the pranlukast group compared to the placebo group. Development of nasal symptoms (sneezing, runny nose and nasal congestion) and disturbance of daily activities were significantly delayed in the pranlukast group. No serious adverse reactions occurred in the pranlukast group and no patient withdrew from treatment with pranlukast.

Conclusions: Pranlukast is effective for prophylactic treatment of pollinosis.

KEY WORDS

allergic rhinitis, Japanese cedar, leukotriene receptor antagonist, pollinosis, prophylactic treatment

INTRODUCTION

Japanese cedar pollinosis is a seasonal allergic rhinitis that has been increasing in prevalence since it was first reported in 1964.[1] The disease is specific to Japan and many patients are found in areas from Kanto to Tokai District along the Pacific Ocean due to the plantation of cedar after the end of World War II. The prevalence of Japanese cedar pollinosis in 2008 was 26.5% across Japan and 32.1% in Tokyo, the area of this study, and has increased by approximately 10% over the past 10 years.[2] The dispersal of Japanese cedar pollen begins in early February, reaches a peak from late February to mid-March, and ends in late March. Patients with Japanese cedar pollinosis often have severe nasal and eye symptoms, which impair their quality of life (QOL) and social productivity.[3] Therefore, it is important to treat patients prior to or at the start of pollen dispersal to prevent pollinosis symptoms in the peak dispersal season. Based on these criteria, the Japanese clinical guidelines for nasal allergy recommend early pharmacotherapy for patients with pollinosis.[4]

Leukotriene receptor antagonists (LTRAs) reduce cysteinylleukotriene (cysLT)-induced vasodilation[5] and vascular hyperpermeability[6] in the nasal mucosa

[1]Department of Otorhinolaryngology and [2]Department of Pharmacology, Nippon Medical School, Tokyo, Japan.
Correspondence: Minoru Gotoh, Department of Otorhinolaryngology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan.
Email: m.gotoh@nms.ac.jp
Received 22 October 2010. Accepted for publication 25 February 2011.

and are effective for nasal congestion.[7,8] CysLTs also stimulate release of inflammatory cells, including eosinophils and macrophages,[9,10] and LTRAs are effective for allergic inflammation caused by these cells in patients with perennial allergic rhinitis.[11] Many clinical studies have shown that LTRAs have a similar effect to antihistamines in patients with pollinosis.[12-14] Overseas[15] and Japanese[16,17] studies have shown that LTRA administration prior to or in the early period of pollen dispersal reduces symptoms during pollen dispersal. Prophylactic treatment of pollinosis should be performed with a minimum number of different types of drugs and the therapy should delay the onset of symptoms and impairment of QOL. In this study, we evaluated the efficacy of pranlukast, a LTRA, for prophylactic treatment of pollinosis based on these criteria.

METHODS

SUBJECTS

The subjects were patients with Japanese cedar pollinosis who lived in Tokyo and surrounding areas. The inclusion criteria were an age of 20-65 years old, a positive result (eruption diameter ≥10 mm) in the antigen-specific dermal test for standard Japanese cedar pollen extracts (Torii Pharmaceutical Co., Tokyo, Japan), or a serum Japanese cedar-specific IgE level ≥2 in a CAP radioallergosorbent test (SRL Inc., Tokyo, Japan). The exclusion criteria were complication with nasal polyp, acute/chronic rhinitis, or sinusitis; a requirement for continuous administration of antihistamines, antiallergic drugs or a steroid nasal spray; current immunotherapy; pregnant/lactating women, or patients who planned to become pregnant; or persons judged by a physician to be inappropriate from an efficacy and safety perspective. After a full explanation of the study and expected adverse reactions was given, informed consent was obtained from each patient. This study was conducted in Nippon Medical School Hospital in accordance with the Helsinki Declaration (2000) and ethical guidelines for clinical trials, after approval of the Nippon Medical School Hospital Ethics Committee.

STUDY PROTOCOL

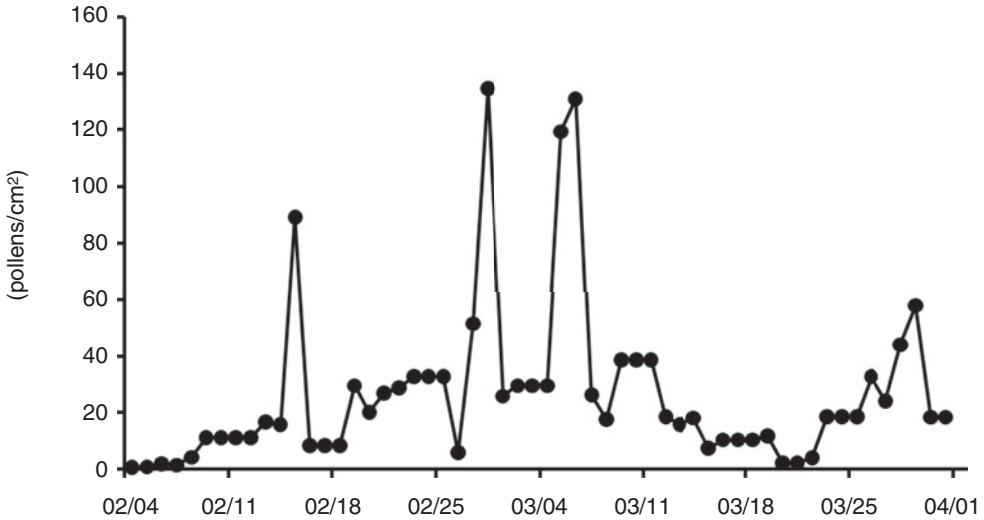
Pranlukast hydrate (112.5 mg) or placebo in a capsule was used in the study. The placebo and 112.5 mg pranlukast capsule were confirmed to be indistinguishable by the controller of the study. Subjects who had given consent were allocated to placebo and pranlukast groups at random. This was done in groups of six patients, with three placed in the placebo group and three in the pranlukast group, without bias in sex and age. At the end of January 2007, 89 patients (41 in the placebo group and 48 in the pranlukast group) with a skin test positive for Japanese cedar pollen were selected among the 97 participants who had initially been allocated to the groups. In accordance with the study schedule shown in Figure 1, pranlukast or placebo was administered from February 4. Patients took 2 capsules orally twice a day after breakfast and supper for 4 weeks (double blind study period). Subsequently, all patients were given pranlukast for 4 weeks (pranlukast treatment period).

From two weeks after the start of the study, the patients were allowed treatment based on their own judgment and in accordance with the clinical guidelines for nasal allergy. Thus, patients were allowed to use an antihistamine (loratadine, 1 tablet/day), a vasoconstrictor nasal spray (tetrahydrozoline hydrochloride, up to 2 sprays in each nostril/day for no more than 7 continuous days), and cromolyn sodium eye drops (up to 4 drops in each eye) during and after the second half of the double blind study period. During the pranlukast administration period (Fig. 1), patients were also allowed to use these drugs and a steroid nasal spray (fluticasone propionate), again based on the severity of symptoms and their own judgment.

The test products were capsules containing placebo or pranlukast (112.5 mg) and were verified to be indistinguishable from each other by the study controller. Patients were randomly assigned to the pranlukast or placebo group (3 patients/group, 6 patients/set) by the controller without bias in sex and age. Japanese cedar pollen was detected using a Durham pollen sampling device in Chiyoda-ku, Tokyo and the amount of dispersed Japanese cedar pollen was obtained from data published by the Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government.

EVALUATION

The patients completed daily records of nasal allergy diary and answered the Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) every 2 weeks until the end of the study. Nasal symptoms were evaluated from the nasal allergy diary. Paroxysmal sneezing (frequency of sneezing per day), runny nose (frequency of nose blowing per day), nasal congestion, and disturbance of daily activities were evaluated on a 5-point scale (0-4) using Okuda's modified classification. A mean weekly score was calculated for each symptom and for disturbance of daily activities. A score that increased by at least 1 compared to the score in week 1 was taken to indicate the presence of a symptom or worsening of disturbance in daily activities. The percentage of patients who did not need a concomitant drug was also determined from the daily nasal allergy records. The QOL items of the JRQLQ and overall conditions based on the face scale were rated on a 5-point scale (0-4). A score that was at least 1 point higher than the score at the start of the study was taken to indicate impairment of QOL or of overall conditions.



	4 Feb - 3 Mar (double blind study period)		4 Mar - 31 Mar (pranlukast administration period)
Placebo group	Placebo		Pranlukast
Pranlukast group	Pranlukast		
Rescue drug	None	Antihistamine Vasoconstrictor nasal spray Cromolyn sodium eye drops	Antihistamine Vasoconstrictor nasal spray Steroid nasal spray Cromolyn sodium eye drops

Fig. 1 Study schedule and the amount of cedar pollen dispersed in 2007.

STATISTICAL ANALYSIS

Data analysis was conducted using chi-square and log-rank tests with two-tailed distributions and a significance level of 5%, using SAS v. 8.02 (Cary, NC, USA).

RESULTS

AMOUNT OF CEDAR POLLEN DISPERSAL

As shown in Figure 1, pollen dispersal in 2007 started on February 6 (2 days after the start of administration) and the amount of cedar pollen exceeded 20/cm^2/day almost daily for 3 weeks from February 19 to March 11. Pollen gradually decreased from March 12 onwards and was rarely detected on April 1 and thereafter. The total amount of cedar pollen from February 4 to March 31 was 1329/cm^2.[18]

SUBJECTS

Of the initial 89 patients, 87 completed the study and 2 were omitted: one due to pregnancy and the other due to withdrawal of agreement. The placebo group consisted of 39 patients (22 males, 17 females, age 35.8 ± 12.4 years old) and the pranlukast group included 48 patients (30 males, 18 females, age 36.7 ± 11.4 years old). The rates of perennial allergic rhinitis were 35.9% and 27.1% in the placebo and pranlukast groups, respectively. There was no significant difference in sex, age, age of incidence, duration of disorder, and frequency of perennial allergic rhinitis between the two groups (Table 1).

THERAPEUTIC EFFECT

Onset of sneezing, runny nose and nasal congestion, and disturbance of daily activities were significantly delayed in the pranlukast group compared with the control group (Fig. 2). The rates of appearance of sneezing, runny nose, and nasal congestion and disturbance of daily activities were significantly lower in the pranlukast group compared to the placebo group at the end of the double blind period and at the end of the study (χ^2-test and data not shown). Use of concomitant antihistamines, steroid nasal spray, and cromolyn sodium eye drops showed similar courses in the pranlukast and placebo groups, but the use of a vasoconstrictor nasal spray was significantly delayed in the pranlukast group compared with the placebo group (Fig. 3). In the 4-week double blind study, a significantly higher percentage of patients in the pranlukast group did not need a concomitant nasal

Table 1 Patient backgrounds

	The placebo group (n = 39)	The pranlukast group (n = 48)	p-value
Sex (males/females)	22/17	30/18	0.565 (χ2-test)
Age (years, mean ± S.D.)	35.8 ± 12.4	36.7 ± 11.4	0.720 (t-test)
Age at onset (years, mean ± S.D.)	23.7 ± 9.7	25.4 ± 9.2	0.407 (t-test)
Duration of disease (years, mean ± S.D.)	12.1 ± 8.3	11.5 ± 8.7	0.771 (t-test)
Perennial allergic rhinitis (Complication ratio)	14 (35.9)	13 (27.1)	0.377 (χ2-test)

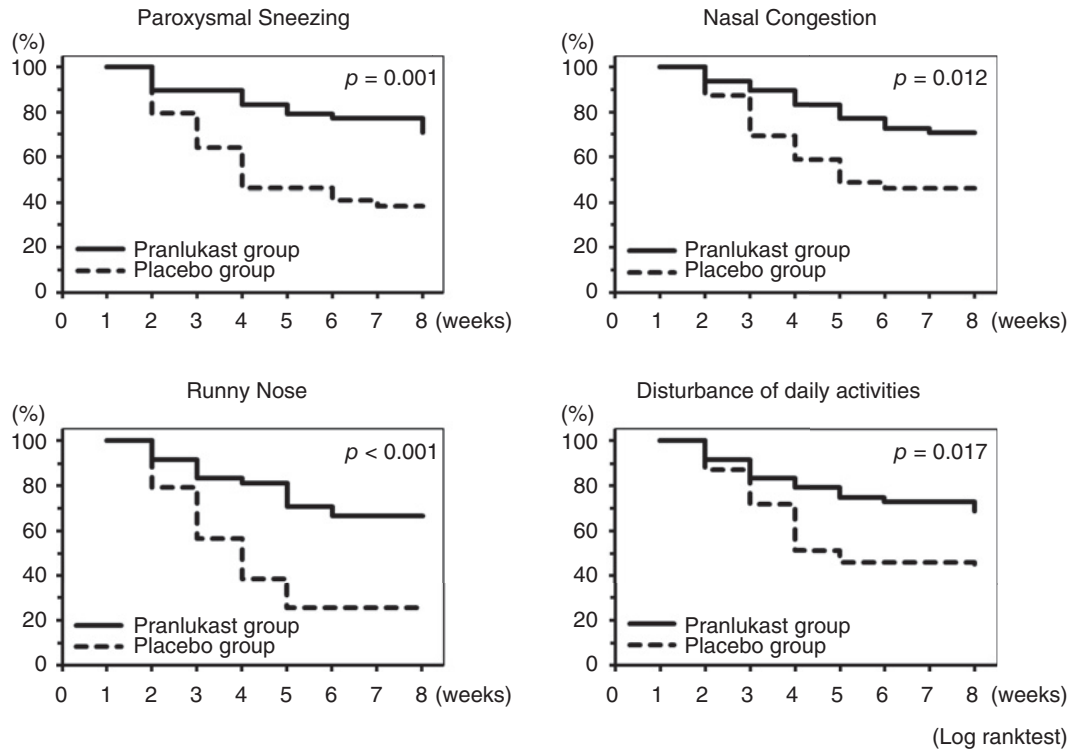


Fig. 2 Changes in the percentage of patients without nasal symptoms or disturbance of daily activities. The mean weekly score was calculated for each symptom and for disturbance of daily activities. A patient with a score that increased by at least 1 from the score in the 1st week was defined as having the symptom or worsening of disturbance in daily activities.

drug (68.8% (33/48) vs. 38.5% (9/39), p = 0.0050, χ^2-test).

With regard to QOL, worsening of scores for eight out of 17 JRQLQ items (disturbance in study, work and housekeeping, poor concentration, reduced thinking, disturbance in reading newspaper/books, memory decline, disturbance in outdoor activities such as sports and picnics, malaise, and fatigue) and for overall conditions were significantly delayed in the pranlukast group compared with the placebo group (Fig. 4). Deterioration of 8 QOL items and the items summarized above were significantly lower in the pranlukast group compared to the placebo group at the end of the double blind period and at the end of the study (χ^2-test and data not shown).

Few patients had new symptoms or newly deteriorated QOL in either group after the end of the double blind period. Moreover, the rates of appearance of symptoms and deterioration of QOL changed similarly in the two groups after the end of the double blind period.

ADVERSE REACTIONS

Two patients in the pranlukast group had adverse reactions. Soft feces occurred 16 days after the start of administration in one patient. The symptom was relieved by 2-day withdrawal and administration of an intestinal regulator, and subsequently pranlukast was resumed and administered continuously. Abdominal pain developed 16 days after the start of administra-

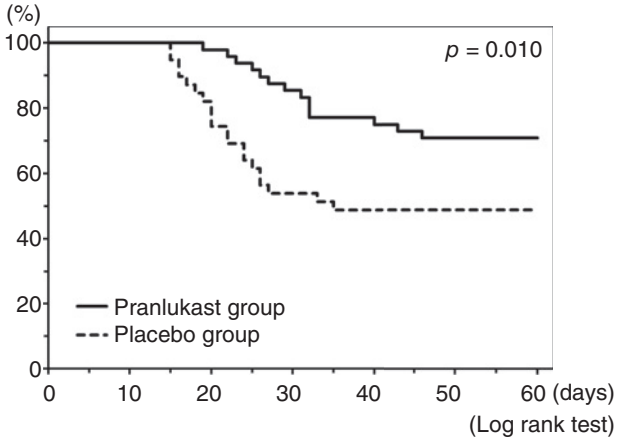


Fig. 3 Changes in the percentage of patients who did not need vasoconstrictor nasal spray. The use of vasoconstrictor nasal spray was determined from the daily records of nasal allergy kept by the patients.

tion in another patient, and disappeared 2 days later without the withdrawal of pranlukast.

DISCUSSION

Several studies have proposed the hypothesis of "minimal persistent inflammation" in allergic rhinitis,[19,20] with repeated exposure to antigens at a low level (that does not induce symptoms in a single exposure) suggested to cause persistent nasal inflammation. Patients with seasonal allergic rhinitis are repeatedly exposed to antigens at one-hundredth the level that induces symptoms in the off-season, and this causes increased histamine and ECP concentrations in nasal discharge.[21] Furthermore, IL-1, leukotriene and ECP in nasal discharge remain high even after improvement of symptoms to preseason levels at 6 weeks after the end of the pollen season.[22] The hypothesis of "minimal persistent inflammation" suggests that administration of antiinflammatory drugs to patients with pollinosis prior to or in the early period of pollen dispersal is important for inhibition of

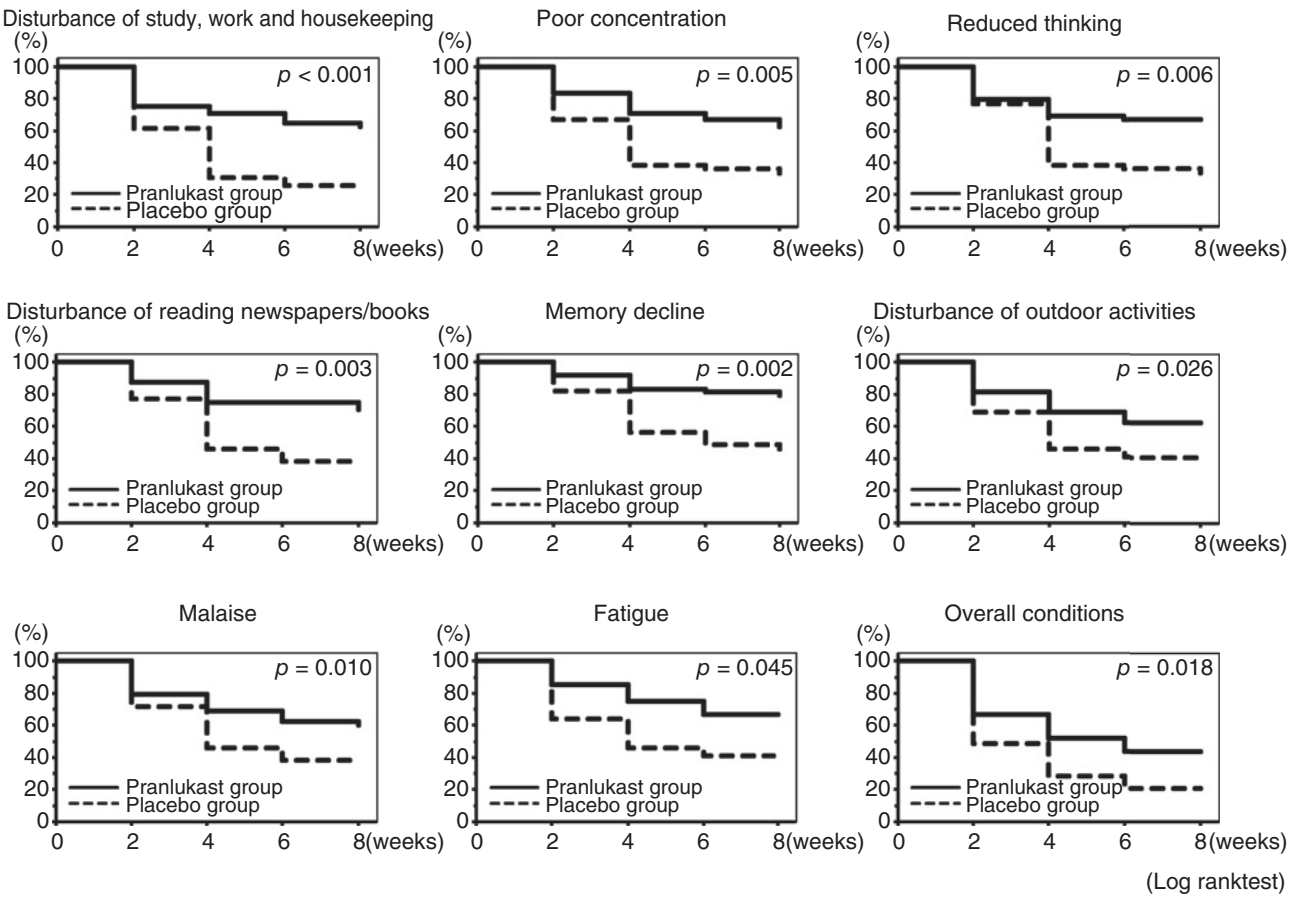


Fig. 4 Changes in the percentage of patients who showed no worsening of QOL and overall conditions. The QOL domains of the JRQLQ and overall conditions based on the face scale were rated on a 5-point scale (0-4). A patient with a score that increased by at least 1 from the score at the start of the study was defined as having worsening of QOL or worsening of overall conditions.

symptoms and minimization of QOL disturbance in the pollen dispersal season.

Several placebo-controlled comparative studies have shown the efficacy of treatment of pollinosis with LTRAs in the early season based on nasal symptom and QOL scores; i.e., these scores in the treated group were better than those in the placebo group.[13-15] In prophylactic treatment of pollinosis, it is important to delay the onset of nasal symptoms and QOL impairment, and it is also better to treat patients with fewer kinds of drugs. Thus, in this study we evaluated the appropriateness of pranlukast for prophylactic treatment of pollinosis based on these criteria. Prophylactic treatment with pranlukast was found to delay onset of nasal symptoms, including sneezing, runny nose and nasal congestion, and disturbance of QOL, as evaluated with a QOL questionnaire specific to allergic rhinitis. During the double blind study period, rhinitis was treated effectively with pranlukast alone in approximately 70% of patients. Consequently, we suggest that pranlukast is appropriate for prophylactic treatment of pollinosis.

Only a small number of patients developed new symptoms or showed deteriorated QOL in the pranlukast and placebo groups after the end of the double blind period. The rate of appearance of symptoms and the rate of deterioration of QOL were similar in the two groups after the end of the double blind period.

We believe that these results reflect the effect of use of pranlukast in the two groups after the end of the double blind period, in addition to the effects of combination drugs (especially nasal steroids). Steroid nasal spray is the most effective drug for allergic rhinitis,[23,24] but compliance is sometimes poor and many Japanese patients prefer oral drugs.[25] A combination of an antihistamine and a LTRA has been shown to have a similar effect to steroid nasal spray on daytime nasal symptoms,[26] and the combination therapy may be an option for patients with poor compliance.

Although this study was a small-scale trial, our results show that prophylactic treatment with pranlukast, a LTRA, delayed the incidence of nasal symptoms, worsening of QOL, and use of concomitant drugs. A large-scale comparative trial of the effect of a combination of an antihistamine and LTRA with that of a steroid nasal spray during pollen dispersal is required to confirm these findings. However, we conclude that LTRAs are appropriate drugs for prophylactic treatment of Japanese cedar pollinosis.

ACKNOWLEDGEMENTS

We appreciate the advice of Drs. Minoru Okuda, Akiyoshi Konno, Yoshitaka Okamoto and Peary L. Orga, and the assistance of Dr. Hidenori Suzuki, who served as the controller of the trial, and Mr. Tatsuyuki Kakuma, the biological statistician. This work was supported by the Japan Allergy Foundation.

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

REFERENCES

1. Horiguchi S, Saito Y. [Discovery of Japanese cedar pollinosis in Nikko, Ibaraki prefecture]. *Arerugi* 1964;**13**:16-8 (in Japanese).
2. Murayama K, Baba K, Okubo K. [Regional differences in the prevalence of Japanese cedar-pollen allergy]. *Arerugi* 2010;**59**:47-54(in Japanese).
3. Okubo K, Gotoh M, Shimada K, Ritsu M, Okuda M, Crawford B. Fexofenadine improves the quality of life and work productivity in Japanese patients with seasonal allergic rhinitis during the peak cedar pollinosis season. *Int Arch Allergy Immunol* 2005;**136**:148-54.
4. *[Practical Guidelines for the Management of Allergic Rhinitis in Japan: Perennial Rhinitis and Pollinosis],* 6th edn. Tokyo: Life Science Publishing, 2009(in Japanese).
5. Mizutani N, Nabe T, Imai A, Sakurai H, Takenaka H, Kohno S. Markedly increased nasal blockage by intranasal leukotriene D4 in an experimental allergic rhinitis model: contribution of dilated mucosal blood vessels. *Jpn J Pharmacol* 2001;**86**:170-82.
6. Shirasaki H, Kojima T, Asakura K, Kataura A, Shimamoto K, Iimura O. The pathophysiological role of kinin and chemical mediators on experimental allergic rhinitis. *Adv Exp Med Biol* 1989;**247A**:375-8.
7. Lipworth BJ. Emerging role of antileukotriene therapy in allergic rhinitis. *Clin Exp Allergy* 2001;**31**:1813-21.
8. Meltzer EO. Clinical evidence for antileukotriene therapy in the management of allergic rhinitis. *Ann Allergy Asthma Immunol* 2002;**88**(Suppl 1):23-9.
9. Oshima N, Nagase H, Koshino T *et al.* A functional study on CysLT(1) receptors in human eosinophils. *Int Arch Allergy Immunol* 2002;**129**:67-75.
10. Thivierge M, Stankova J, Rola-Plerszczynski M. IL-13 and IL-4 upregulate cysteinyl leukotriene 1 receptor expression in human monocytes and macrophages. *J Immunol* 2001;**167**:2855-60.
11. Ueda T, Takeno S, Furukido K, Hirakawa K, Yajin K. Leukotriene receptor antagonist pranlukast suppresses eosinophil infiltration and cytokine production in human nasal mucosa of perennial allergic rhinitis. *Ann Otol Rhinol Laryngol* 2003;**112**:955-61.
12. Philip G, Malmstrom K, Hampel FC *et al.* Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002;**32**:1020-8.
13. Van Adelsberg J, Philip G, Pedinoff AJ *et al.* Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy* 2003;**58**:1268-76.
14. Meltzer EO, Philip G, Weinstein SF *et al.* Montelukast effectively treats the nighttime impact of seasonal allergic rhinitis. *Am J Rhinol* 2005;**19**:591-8.
15. Kurowski M, Kuna P, Gorski P. Montelukast plus cetirizine in the prophylactic treatment of seasonal allergic rhinitis: influence on clinical symptoms and nasal allergic inflammation. *Allergy* 2004;**59**:280-8.
16. Sasaki K, Okamoto Y, Yonekura S *et al.* Cedar and cypress pollinosis and allergic rhinitis: Quality of life effects of early intervention with leukotriene receptor antagonists. *Int Arch Allergy Immunol* 2009;**149**:350-8.
17. Yonekura S, Okamoto Y, Okubo K *et al.* Beneficial effects

of leukotriene receptor antagonists in the prevention of cedar pollinosis in a community setting. *J Investig Allergol Clin Immunol* 2009;**19**:195-203.
18. Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government. [Data for Japanese Cedar Pollen]. Available at: http:www.fukushihoken.metro.tokyo.jp/kanho/kafun/kousin/sugi.html(in Japanese).
19. Storms WW. Minimal persistent inflammation, an emerging concept in the nature and treatment of allergic rhinitis: the possible role of leukotrienes. *Ann Allergy Asthma Immunol* 2003;**91**:131-40.
20. Canonica GW, Compalati E. Minimal persistent inflammation in allergic rhinitis: implications for current treatment strategies. *Clin Exp Immunol* 2009;**158**:260-71.
21. Roquat A, Ihre E, van Hage-Hamsten M, Halldén G, Zetterström O. Allergen-induced inflammation in the nose: a comparison of acute and repeated low-dose allergen exposure. *Allergy* 1996;**51**:42-8.
22. Bachert C, van Kempen M, van Cauwenberge P. Regulation of proinflammatory cytokines in seasonal allergic rhinitis. *Int Arch Allergy Immunol* 1999;**118**:375-9.
23. Bhatia S, Baroody FM, DeTineo M, Naclerio RM. Increased nasal airflow with budesonide compared with desloratadine during the allergy season. *Arch Otolaryngol Head Neck Surg* 2005;**131**:223-8.
24. Berger WE, Nayak AS, Staudinger HW. Mometasone furoate improves congestion in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Pharmacother* 2005; **39**:1984-9.
25. Okuda M, Ohkubo K, Gotoh M, Ishida Y. [Treatment of Japanese cedar pollinosis and its impact on patients satisfaction]. *Arerugi* 2004;**53**:596-600(in Japanese).
26. Wilson AM, Orr LC, Sims EJ, Lipworth BJ. Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. *Clin Exp Allergy* 2001;**31**:61-8.